Toxic Shock Syndrome

	Title of Guideline	**Guideline for the identification and management of Toxic Shock Syndrome in Children and Young People**
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	Directorate & Speciality	Directorate: Family Health – Paediatrics Speciality: Infections and Immunology
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	Explicit definition of patient group to which it applies (e.g. inclusion and exclusion criteria, diagnosis)	Children and young people under the age of 18 years presenting with cardiovascular collapse and/or sepsis
	Key Words	Paediatrics. Children. Toxic Shock. Sepsis. Intravenous Immunoglobulin. IVIG. Shock. Hypotension
	Statement of the evidence base of the guideline – has the guideline been peer reviewed by colleagues?	
1a	meta-analysis of randomised controlled trials	Put a cross (X) in the highest level of evidence.
1b	At least one randomised controlled trial	
2a	at least one well-designed controlled study without randomisation	
2b	at least one other type of well-designed quasi-experimental study	
3	well –designed non-experimental descriptive studies (i.e. comparative / correlation and case studies)	X
4	expert committee reports or opinions and / or clinical experiences of respected authorities	
5	recommended best practise based on the clinical experience of the guideline developer	
	Consultation Process	Staff at Nottingham Children's Hospital via the Guidelines E-mail process.
	Target audience	Staff at the Nottingham Children's Hospital
	This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date.	

Document Control

Document Amendment Record

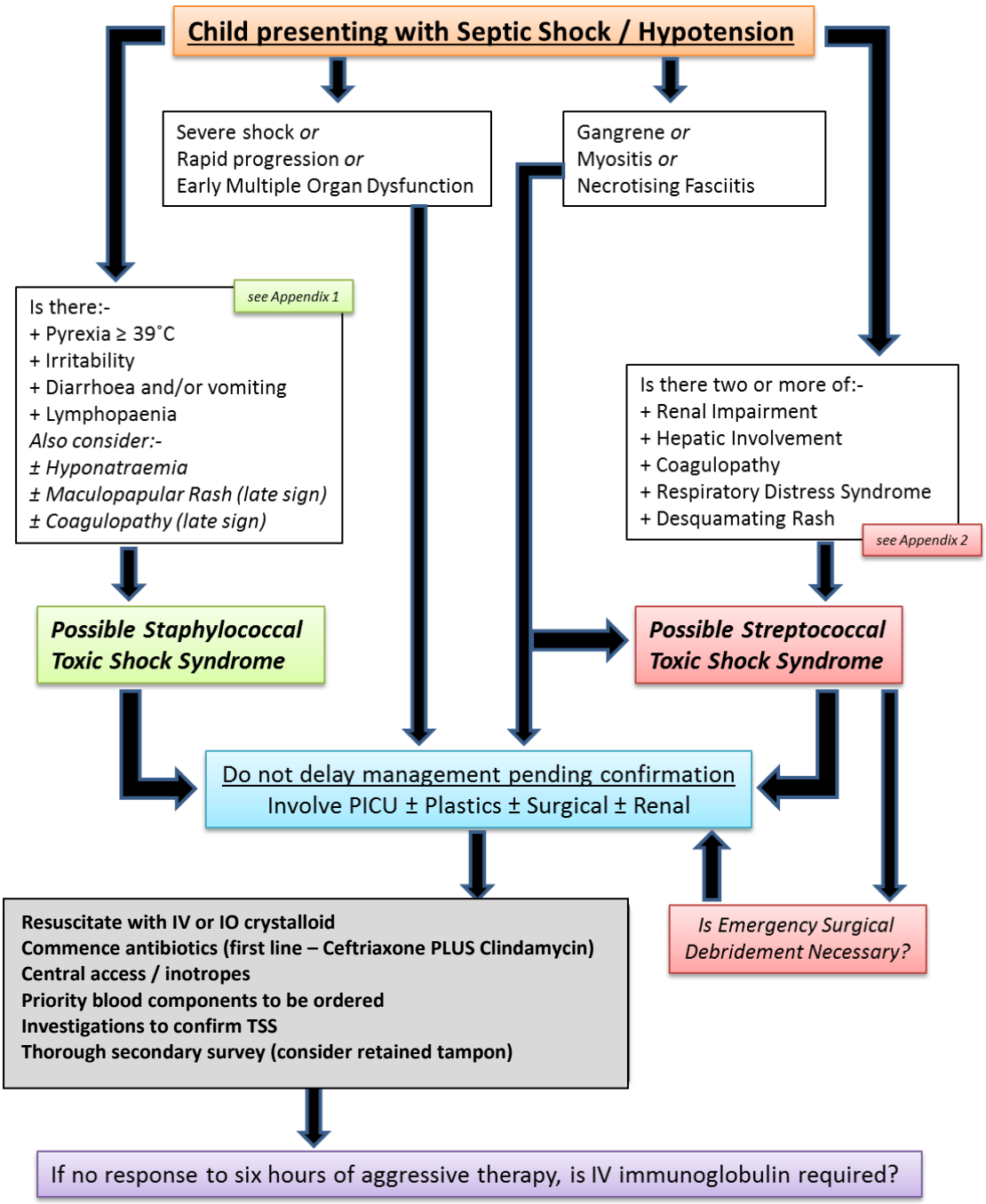
Version	Issue Date	Author
V1	July 2013	Dr Benjamin Davis, Paediatric Trainee Prof Harish Vyas, PICU Consultant
V2	December 2019	Dr Jon Davies, Consultant Paediatric Anaesthetist Dr Craig Stewart, Paediatric Critical Care Trainee

Summary of changes for new version:

- Updated references
- Burns injury wound care
- Change of fluid for resuscitation from 4.5% HAS to crystalloids (as per high risk sepsis guideline)

Statement of Compliance with Child Health Guidelines SOP
This guideline has followed Child Health Guideline SOP. It has been circulated to all Paediatric Senior staff and comments incorporated before uploading to the Trust Guideline site.
Maria Moran
Clinical Guideline Lead
31 January 2020

Diagnosis and Management of Toxic Shock Syndrome in Children – Summary Flowsheet



Don't forget to complete IVIG form – but do not delay administration Click on this link for direct access to the request form http://qpharmsql1/ivig/ else follow:-

NUHnet -> Diagnostics & Clinical Support -> Pharmacy -> Drugs and Therapeutics -> Immunoglobulin Website, on the Intranet; and click on **Immunoglobulin Request Form** under the key documents.

Introduction / Background

Toxic Shock Syndrome (TSS) is a rare acute, multi-system, exotoxin-mediated illness which typically results in shock and multi-organ failure early in its clinical course. Causes include toxin-producing strains of *Staphylococcus aureus* and Invasive Group A Streptococcus (e.g. *Streptococcus pyogenes*).

Staphylococcus produces virulence factors such as protein A, capsular polysaccharides and α toxin. Some strains produce toxic shock syndrome toxin 1 (TSST-1), Panton-Valentine Leucocidin (PVL) and other toxins[1]. Staphylococcal TSS is most commonly associated with disruption of skin and mucous membranes – especially unhealed burns and surgical wounds (within a few days of injury). No clear source of infection may be identified however. There are also associations with tampons ('menstrual' TSS), tracheitis, pneumonia and empyema.

Group A Streptococci are a common commensal of skin and throat. Invasive Group A Streptococcal disease (iGAS) is the invasion of Group A Streptococcus into a normally sterile site, for example septic arthritis, puerperal sepsis, peritonitis and necrotising fasciitis. Toxic Shock Syndrome is a superantigen-mediated complication rarely associated with iGAS.

The overall incidence of TSS children in the UK & the Republic of Ireland has been estimated to be 0.38 per 100,000 children[2].

Clinical Assessment

Toxic Shock Syndrome may be indistinguishable in its initial stages from other childhood illness (including Scarlet fever, Kawasaki disease, Meningococcaemia, Stevens-Johnson and Staphylococcal scalded skin syndrome). A non-specific prodrome (consisting of fever, myalgia and gastro-intestinal upset) rapidly progresses to agitation, confusion and lethargy. Patients are typically markedly hypotensive at presentation. Unhealed burns should prompt consideration of TSS. Typical cases of TSS secondary to a burn may present within 2 days of a thermal injury, in a child under 2 years old with a burn of less than 10% of body surface area[3]. However a child may become unwell with a burn injury of any size[4].

The diagnosis of Toxic Shock Syndrome in children is a clinical one. Clinical suspicion of TSS should be raised in cases of paediatric sepsis with an early component of severe shock progressing to multi-organ dysfunction.

N.B. – Do not delay treatment in suspected cases of toxic shock syndrome whilst awaiting laboratory confirmation. Staphylococcal TSS is rapidly progressive with an estimated mortality of between 20-50%[3 4 5] while Streptococcal TSS is estimated to have an even higher mortality[6].

Diagnosis

Staphylococcal Toxic Shock Syndrome

Using the criteria for case definition of Staphylococcal Toxic Shock Syndrome[7 8] in paediatric practice is complicated by communication difficulties, diminished prodromal period in children and the requirement to include desquamation in the diagnosis (this occurs up to two weeks later and only if the illness is allowed to progress).

Pragmatic criteria for diagnosis of Staphylococcal TSS in children[4] include:-

1. Pyrexia ≥ 39°C
2. Irritability
3. Diarrhoea +/- vomiting
4. Lymphopaenia with a commonly normal total white cell count
5. Rash (commonly non-specific diffuse maculopapular)

Not all of these features need to be present to make the diagnosis.

Hyponatraemia is commonly seen. Other haematological changes such as thrombocytopaenia and coagulopathy may be late developments in children.

Streptococcal Toxic Shock Syndrome

Streptococcal TSS commonly arises from invasive soft tissue infections *viz.* necrotising fasciitis, cellulitis and myositis. Diagnosis is confirmed by the isolation of Group A *Streptococcus* from a normally sterile site (blood, CSF, peritoneal fluid, tissue biopsy) together with clinical signs of severity[9]:-

- Hypotension / shock
- Two or more of the following:-
    - Renal impairment
    - Coagulopathy (thrombocytopaenia or disseminated intravascular coagulation)
    - Hepatic involvement (elevated transaminases and bilirubin)
    - Respiratory Distress Syndrome
    - Generalised erythematous, macular rash (may desquamate)
    - Soft tissue necrosis (gangrene, necrotising fasciitis, myositis)

In children, coagulopathy and rash may be late signs and should not be relied upon.

Investigations

Investigations should include:-

- FBC, U&E, Serum Osmolality, Coagulation, LFT's, Blood Gas, Serum Myoglobin, CK
- Blood Culture / Sensitivity
- Urine Dip and Culture / Sensitivity; Urinary Electrolytes and Osmolality
- Stool Culture / Sensitivity
- Swabs – wound, skin, nose, throat (special request of Staphylococcal phage type and toxin production (TSST-1))
- Staphylococcal antibody assay (0.125ml serum sample)
- PCR for Staphylococcal toxogenicity (0.1ml serum sample)

The last two samples should be sent to microbiology who will forward to Public Health.

Management

TSS is rapidly progressive with high mortality. Suspected cases should be managed on the Paediatric Intensive Care Unit. Consultant advice and support should be sought from the PICU, Burns and Paediatric Renal teams.

Supportive Management

Management as per standard NICE high risk sepsis guidelines[10] should be commenced including active fluid resuscitation, early use of vasoactive drugs, establishment of central access and intubation / mechanical ventilation if required. Note that unlike "warm shock" TSS usually displays high systemic vascular resistance and may be refractory to inotropes.

Fluids

Crystalloids such as Plasma-Lyte 148 or Sodium Chloride 0.9% are appropriate for initial resuscitation but blood components including red cells and fresh frozen plasma (FFP) should be arranged as a priority. Maintenance fluids should be restricted to 80% of normal requirements. Hyponatraemia and osmolality will require correction.

Causes and Source Control

Ensure a careful survey for infectious focus. Any surgical wounds should be considered potential sources of infection. If evidence of wound infection, wide debridement is suggested. Do not delay surgical intervention for medical imaging. Necrotising fasciitis or necrotising myositis is a surgical emergency requiring aggressive debridement. In females, vaginal examination for foreign bodies such as tampons should be considered.

Burns Injuries Wound Care

Swab the wound as above and gently clean with a diluted antiseptic solution and gauze, then apply a non-adherent antimicrobial dressing. Advice should be sought from the paediatric burns team.

Antimicrobial Therapy

Administration of antibiotics is used to lessen bacterial load, inhibit further bacterial colonisation and reduce toxin production. Inadequate initial antimicrobial therapy markedly increases mortality.

Initial antibiotic therapy should follow the NUH Paediatric High Risk Sepsis guidelines with empirical therapy to cover both gram positive and gram negative organisms until a diagnosis is confirmed. As such Ceftriaxone 100mg/kg (max 4g) once daily PLUS Clindamycin 10mg/kg (max 1.2g) should be started as first line agents. Note that Ceftriaxone should not be used with calcium containing infusions (such as for patients requiring calcium corrections whilst on inotropes) or parenteral nutrition, instead use Cefotaxime 50mg/kg (max 3g) every 6 hours.

If a diagnosis of TSS is confirmed or considered highly likely, for example with evidence of a skin and soft tissue infection following a burn, then specific cover for both Staphylococcal TSS and Group A Streptococcal disease with Flucloxacillin 50 mg/kg and Clindamycin is advised.

For patients with history of penicillin allergy discuss with microbiology.

Vancomycin is not advised as a first-line antibiotic due to the low prevalence of MRSA in the paediatric population.

Please see NUH Paediatric High Risk Sepsis guidelines for further details and discuss each case with microbiology at the earliest opportunity.

Intravenous Immunoglobulin (IVIG)

IVIG is recommended as an adjunctive therapy in children with severe toxin-related infection showing failure to improve despite best standard care[11]. However, there have been no controlled trials of IVIG therapy in staphylococcal TSS; data is limited to case reports and retrospective reviews. Intravenous immunoglobulin should be considered in patients where there has been no clinical response within the first six hours of aggressive therapy[12]. IVIG for this indication should be at the request of a PICU Consultant only. NHS England has issued new commissioning criteria and guidelines for the use of immunoglobulins, effective across NUH from April 2019. An IVIG request form must be submitted to the immunoglobulin panel (see link above).

There is no conclusive evidence or guideline for IVIG dosage for this indication. Therefore adoption of the recommended dose for PVL-SA / adult TSS is recommended. Total dose of 2g/kg is suggested – see PICU Immunoglobulin

pharmacopeia (link NUHnet -> Guidelines -> Paediatrics -> PICU Pharmacopeia) for dosing, prescribing and administration. It is reasonable to consider repeat administration after 48 hours if there remains a poor response to treatment but this will require further panel approval.

Human Intravenous Immunoglobulin (IVIG) may rarely induce thromboembolic events including myocardial infraction, cerebrovascular accident, pulmonary embolism and deep vein thrombosis. Caution is therefore advised in the prescription and administration of high dose immunoglobulin in patients with pre-existing factors for arterial or venous thrombotic events.

Evidence for the use of IVIG in paediatrics and neonates

Results of trials on intravenous immunoglobulin (IVIG) as adjunctive therapy for sepsis have been conflicting. A prospective single-centre case-control study suggested IVIG conferred a significant reduction in mortality in PICU sepsis patients[13]; adjunctive use if IVIG in sepsis and septic shock is advocated in the 2008 *Surviving Sepsis* guidelines[14]. However meta-analysis in adults and children has failed to conclusively support the use of IVIG in sepsis and septic shock[15 16]. There is a growing evidence that IVIG therapy has no effect upon the outcome of suspected or proven neonatal sepsis[16 17].

Evidence for the use of IVIG in Staphylococcal Toxic Shock Syndrome in children is graded as III on the basis of case reports, in vitro studies and extrapolation from adult studies[11] and is recommended for use as a short-term therapy of medium (blue) priority in the event of clinical rationing.

Appendix 1 – Criteria for Case Definition for Staphylococcal Toxic Shock Syndrome in Children

- Pyrexia ≥39°C
- Irritability
- Diarrhoea +/- Vomiting
- Lymphopaenia (with usually normal total white cell count)
- Rash (diffuse macular erythroderma with subsequent desquamation)

These five criteria are useful for pragmatic diagnosis in children. Hyponatraemia is another useful indicator. It is important to note that rash and desquamation are late developments. Thrombocytopaenia and coagulopathy may also be seen but are late developments in children.

Note that the isolation of *Staphylococcus* is not required to make the definition of Staphylococcal Toxic Shock Syndrome.

Appendix 2 – Case Definition for Streptococcal Toxic Shock Syndrome in Children

Illness fulfilling criteria IA and II (A and B) can be defined as a definite case

Illness fulfilling criteria IB and II (A and B) can be defined as a probable case if no other aetiology is identified

I Isolation of Group A Streptococci (*Streptococcus pyogenes*)

A – From a normally sterile site (e.g. blood, cerebrospinal fluid, pleural or peritoneal fluid, tissue biopsy, surgical wound, etc.)

or

B – From a non-sterile site (e.g. throat, sputum, vagina, superficial skin lesion, etc.)

II Clinical Signs of Severity

A – Hypotension (systolic blood pressure < 5th percentile for age in children)

and

B – 2 or more of the following:-

1. Renal impairment – creatinine > twice upper limit of normal for age or if pre-existing renal disease, a two-fold elevation over baseline level.
2. Coagulopathy – platelets < $100x10^9$ or disseminated intravascular coagulation (defined by prolonged clotting times, low fibrinogen level and presence of fibrinogen degradation products).

3. Liver involvement – ALT, AST or bilirubin levels > twice upper limit of normal for age. In patients with pre-existing disease, a two-fold elevation over baseline level.
4. Adult Respiratory Distress Syndrome – acute onset of pulmonary infiltrates and hypoxia in the absence of cardiac failure; OR evidence of diffuse capillary leak manifested by acute onset of generalised oedema; OR pleural / peritoneal effusions with hypoalbuminaemia.
5. Generalised erythematous macular rash that may desquamate.
6. Soft tissue necrosis, including necrotising fasciitis, myositis or gangrene.

Risk factors include:-

- Recent *Varicella* infection
- Trauma
- Recent respiratory tract infection (especially influenza)
- Diabetes mellitus
- NSAID use

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